PATENT SPECIFICATION 799,415

Inventors:—SIEGFRIED GOTTFRIED and LILY BAXENDALE.

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International Classification:—A61k.

COMPLETE SPECIFICATION.

Improvements in or relating to Veterinary Compositions.

We, BIOREX LABORATORIES LIMITED, a British Company, of 47/51 Exmouth Street (Mkt.), Rosebery Avenue, London, E.C.1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is for improvements in or relating to veterinary compositions for topical application and has for an object to provide a composition which is advantageous in the treatment of inflammatory diseases in animals.

Where the skin is affected by micro-organisms, chemical irritants or other noxious substances or where there is an organic disfunction resulting in a pathological skin condition, there is an inflammatory condition and a breakdown of the tissues occurs. Instances of such skin affections are the various forms of pruritus affecting birds and both small and large animals, such as dogs, cats and horses.

Certain derivatives of liquorice roots (Glycyrrhiza), generally known as glycyrrhetinic acid and its salts and esters, have been shown to have some action in the body of animals resembling those of cortisone and hydrocortisone substances secreted by the adrenal glands. In particular, Galal has shown (British Journal of Pharmacology & Chemotherapy, 10, 305/1955) that glycyrrhetinic acid has an effect on the retention of fluids in experimental animals. Glycyrrhetinic acid and its derivatives also have a marked effect on tissue granulation and act as a healing decongestant.

We have now found that glycyrrhetinic acid and its salts and esters have a valuable anti-inflammatory action and, therefore, according to the present invention, there is provided a veterinary composition for topical or intramammary application or for application as a pessary, comprising glycyrrhetinic acid or a salt or ester thereof dispersed in a pharmaceutical carrier base, said composition being in the form of an emulsion, lotion, pessary base or powder; the carrier base is pharmacologically inert.

The following Examples will serve to illustrate the present invention, the percentage figures being calculated by weight:—

EXAMPLE 1.

A veterinary pessary was prepared by dispersing glycyrrhetinic acid in cocoa butter to form a composition containing 1% of the glycyrrhetinic acid; the composition is readily mouldable when warm.

EXAMPLE 2.

A veterinary lotion was prepared by dispersing 1% of glycyrrhetinic acid, 10% of polyethylene glycol (molecular weight 400) and 2% of ethyl cellulose in distilled water.

The compositions of the present invention are useful for reducing inflammation and pruritus of the small animals, such as dogs and cats, birds, and the large animals, such as horses; e.g. Dermatitis, Acute Moist Eczema (Wet Eczema), Acanthosis Nigricans, Miliary Eczema (of cats), Pruritus, particularly localised Pruritus, e.g. Traumatic Pruritus of the axilla in short-legged dogs (dachshunds) and Dermatitis, such as Sweet Itch (Summer Itch) in horses. Other conditions as Otitis Externa, Otitis Media, of dogs, cats and other small animals, Conjunctivitis, Keratitis, various dermatoses in small and large animals as well as in birds, all inflammatory skin conditions associated with bacteria, and parasites, infections in animals such as Mange (pigs, cattle, horses and dogs), e.g. Urticarial irritation in cattle.

and Mastitis (i.e. by intramammary application), both acute and chronic. The incorporation of an enzyme, e.g. trypsin, papain, will jointly assist the elimination of tissue debris.

Various pharmacological properties of glycyrrhetinic acid have been reported in the veterinary literature but there has been no indication of the valuable anti-inflammatory properties of glycyrrhetinic acid or its functional derivatives such as its salts and esters.

The carrier base may be either hydrophilic or hydrophobic in character and the composition is useful in reducing inflammation where there is tissue breakdown not only as a result of the action of micro-organisms as above-mentioned but also where allergic conditions exist.

WHAT WE CLAIM IS:—

1. A veterinary composition for topical or intramammary application or for application as a pessary, comprising glycyrrhetinic acid or a salt or ester thereof dispersed in a pharmaceutical carrier base, said composition being in the form of an emulsion, lotion, powder or pessary base.

2. A veterinary composition containing glycyrrhetinic acid substantially as described in any of the Examples.

CARPMAELS & RANSFORD,
Chartered Patent Agents.

PROVISIONAL SPECIFICATION.

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Where the skin is affected by micro-organisms, chemical irritants or other noxious substances or where there is an organic disfunction resulting in a pathological skin condition, there is an inflammatory condition and a breakdown of the tissues occurs. Instances of such skin affections are the various forms of pruritus affecting birds and both small and large animals, such as dogs, cats and horses.

We have found that glycyrrhetinic acid and its functional derivatives have a valuable anti-inflammatory action and according to the present invention, therefore, there is provided a veterinary composition comprising glycyrrhetinic acid or a functional derivative thereof dissolved or dispersed in a pharmaceutical carrier base which may comprise an emulsion, lotion, ointment or powder: the carrier base is pharmacologically inert.

The compositions of the present invention are useful for reducing inflammation and pruritus of the small animals, such as dogs and cats, birds, and the large animals, such as horses; e.g. Dermatitis, Acute Moist Eczema (Wet Eczema), Acanthosis Nigricans, Miliary Eczema (of cats), Pruritus, particularly localized Pruritus, e.g. Traumatic Pruritus of the axilla in short-legged dogs (dachshunds) and Dermatitis, such as Sweet Itch (Summer Itch) in horses. Other conditions as Otitis Externa, Otitis Media, of dogs, cats and other small animals, Conjunctivitis, Keratitis, various dermatoses in small and large animals as well as in birds, all inflammatory skin conditions associated with bacteria, and parasites, infections in animals such as Mange (pigs, cattle, horses and dogs), e.g. Urticarial irritation in cattle, and Mastitis, both acute and chronic. The incorporation of an enzyme, e.g. trypsin, papain, will jointly assist the elimination of tissue debris.

Various pharmacological properties of glycyrrhetinic acid have been reported in the veterinary literature but there has been no indication of the valuable anti-inflammatory properties of glycyrrhetinic acid or its functional derivatives such as its salts and esters.

The carrier base may be either hydrophilic or hydrophobic in character and the composition is useful in reducing inflammation where there is tissue breakdown not only as a result of the action of micro-organisms as above-mentioned but also where allergic conditions exist.

Glycyrrhetinic acid, its salts and its esters have been shown to have some action in the body of animals resembling those of hydrocortisone and cortisone substances secreted by the adrenal glands. In particular, Galal has shown (British Journal of Pharmacology & Chemotherapy, 1955, Vol. 10, P. 305) that glycyrrhetinic acid has an effect on the retention of fluids in experimental animals.

CARPMAELS & RANSFORD,
Chartered Patent Agents and
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PATENT SPECIFICATION

NO DRAWINGS

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International Classification:—C07c,d,g. A61k.

COMPLETE SPECIFICATION

Glycyrrhetinic Acid Derivatives

We, BIOREX LABORATORIES LIMITED, a British Company, of 47/51, Exmouth Street (Mkt), Rosebery Avenue, London, E.C.1, do hereby declare the invntion, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present application is concerned with new and useful salts of glycyrrhetinic acid.

In Parent Specification No. 26453/59 (843,135) there is described and claimed *inter alia* salts of glycyrrhetinic acid with organic bases. Specific examples of such salts mentioned in the parent specification are the piperazine, triethanolamine and N-methyl glucamine salts of glycyrrhetinic acid.

We have found that the salts formed from glycyrrhetinic acid and monoethanolamine, diethanolamine, choline and isoniazide (i.e. isonicotinic acid hydrazide) are especially useful compounds. These new compounds may also be combined with other acids to give compounds such as isoniazide glycyrrhetinate monohydrochloride.

Medical, pharmacological, and veterinary tests and preliminary trials have been carried out with these new compounds on small and large animals, as well as pharmacological trials using mice, rats, guinea pigs and cats. These tests show that the new derivatives are active in suppressing inflammation, that they heal artificial lesions produced on the skin of animals and that they inhibit allergic reactions of injected allergens, such as aspergillus. When applied locally, these new compounds cause rapid subsidence of any inflammation produced by the introduction of irritant substances into the eye of the rabbit. When applied by systemic injection or by oral administration, these new compounds depress the formation of granuloma tissue induced by subcutaneously-implanted cotton wool pellets in rats in the tests described by Meier, R., Schuler W., and Desaulles, P., Experientia, 1950, 6, 469. These new derivatives depress the formation of inflammatory exudate and of the granulomatous membrane in the granuloma pouch test described by Selye, H., Brit. med. J., 1949, 2. 1129.

When injected systemically into B.C.G.-infected guinea pigs, the new derivatives suppress the reaction to intradermally-injected tuberculin in the test described by Lond, D.A., and Miles, A.A., Lancet, 1950, 1, 492.

In addition, when injected parenterally or administered orally, the new derivatives have a mild depressant action in mice and potentiate the actions of central nervous system depressant drugs, such as hexobarbitone.

The new derivatives have mild analgesic and antipyretic actions.

These new compounds are of value in combating inflammatory conditions of all types and denominations, such as inflammatory conditions of the skin, eye, ear, nose, mouth, dental cavities, genitals, rheumatic conditions, rectal conditions, inflammatory and ulcerative conditions of the digestive system, ulcerative colitis, allergic conditions, vaginitis, vulvitis, dysmenorrhoea, metritis, leukorrhoea, mastitis, and other inflammatory processes whether they be primary or of secondary cause, or the results of such cause.

These new compounds have also been found valuable in the treatment of severe emergencies, in which a "shock-like" state occurs, by virtue of their high solubility in water.

These new compounds have also been found of value when injected into inflamed joints and it was found that symptomatic relief was obtained.

In addition, these new compounds are of

value in a number of illnesses where a mild sedative, analgesic, or antipyretic may be indicated.

The glycyrrhetinic acid derivatives according to the present invention inhibit steroids and their metabolism, such as the usual hormonal secretions of glands, by reduction of glandular secretion activity. They are useful in the treatment of ano-genital diseases, such as vulvitis, vaginitis, ulcerations of the vaginal basin and cervix of the uterus, either alone or in association with leucorrhoea, menstrual disfunctions, ano-genital pruritus, and in the treatment of diseases, such as carcinomas, in which the inhibition of steroids or the reduction of hormonal glandular secretion is of therapeutic value, as well as inflammatory and ulcerative conditions of the digestive system.

The new compounds have a potentiating effect, demonstrating synergism with antibiotic drugs, (such as neomycin) keratoplastic drugs, (such as coal tar), keratolytic drugs, (such as salicylic acid), analgesics, antiseptics, bactericides, chemotherapeutics, baceriostatics, anti-histamines, sedatives, fungicides, insecticides, corticosteroids and xanthoglabrol.

Synergism has also been demonstrated in conjunction with corticosteroids such as hydrocortisone, prednisone and prednisolone, in the replacement therapy of adrenalectomised patients, as well as in Addison's disease, disseminated lupus erythematosus and acute bronchial asthma.

In the case of the isonazide derivatives, these products have been shown to have a bacteriostatic action against microbacteria and are especially useful in the treatment of various forms of tuberculosis, having the ideal action of suppressing the inflammatory reaction caused by the tubercle and the bacericidal effect of the isoniazide. They can be administered either alone or in conjunction with other chemotherapeutics or antibiotics, such as streptomycin, or with para-amino salicylic acid and its salts, and the combination is more effective than either drugs used alone. It is also helpful in leprosy, lupus vulgaris, multiple sclerosis and tubercular conditions, either used alone or in conjunction with drugs such as dapsone (or anti-leprosy drugs), sulphonamides, antibiotics, bactericidals and bacteriostatics, and by virtue of the fact of this combination, much swifter action can be obtained than by using any of these drugs on their own.

The new compounds can be incorporated in various therapeutic forms, such as ointments, solutions, injections, emulsions, suspensions, pastes, enemata, cones, cerates, paints, powders, implants, pessaries, suppositories and sprays, all in conjunction with suitable carriers.

Furthermore, the choline salts and ethanolamine salts are particularly useful for inhibiting allergic reactions and anaphylaxis and have application in such conditions as hay fever, asthma, bonchitis, bronchospasm, bronchiectasis, uticaria and other allergic conditions. They may also be useful in the treatment of inflammatory conditions occasioned by, for example, coronary arterosclerosis and hepatic cirrhosis.

The new compounds according to the present invention may be prepared by any of the usual methods for preparing salts, such as the reaction of glysyrrhetinic acid with the corresponding base or by double decomposition.

The following examples are given for the purpose of illustrating the present invention.

Example 1

4.7 g. glycyrrhetinic acid were dissolved in the minimum amount of ethanol and 1.37 g. isoniazide were then added thereto. The reaction mixture was evaporated to dryness and the salt obtained recrystallised from aqueous methanol. Isoniazide glycyrrhetinate was obtained in the form of colourless soft needles; m.p. 292—294° C.; $[\alpha]_D = +162°$ (1% in chloroform).

Example 2

1 g. isoniazide glycyrrhetinate, obtained as in Example 1, was dissolved in methanol and an exactly equivalent amount of hydrogen chloride in the form of a dilute aqueous solution was added. The mixture was evaporated to dryness to give the hydrochloride of isoniazide glycyrrhetinate in the form of a white soft powder, m.p. 285—290° C.; $[\alpha-]_D = +150°$ (1% in chloroform).

Example 3

4.7 g. glycyrrhetinic acid were dissolved in the minimum quantity of chloroform and 20 cc. ethanol added followed by 5.5 cc. of a 60% solution of choline bicarbonate in water. The mixture was evaporated to dryness, giving the choline salt of glycyrrhetinic acid in the form of a white powder.

Example 4

3.1 g. monoethanolamine in 30 cc. chloroform were added to 23.5 g. glycyrrhetinic acid previously dissolved in 100 cc. chloroform. After warming to 50° C. and shaking for a few minutes, the suspension was filtered and the filtrate evaporated on a water bath. The residue was the monoethanolamine salt of glycyrrhetinic acid which is a non-water-soluble white powder, m.p. 150° C.

The diethanolamine salt was prepared in the same manner, but using 5.3 g. diethanolamine in 50 cc. chloroform.

WHAT WE CLAIM IS:—

1. Monoethanolamine glycyrrhetinate.
2. Diethanolamine glycyrrhetinate.
3. Choline glycyrrhetinate.
4. Isoniazide glycyrrhetinate and the monohydrochloride thereof.
5. Process for the preparation of salts of

glycyrrhetinic acid according to any of Claims 1—4, wherein said salts are prepared from glycyrrhetinic acid by methods known *per se* for the conversion of organic acids to their salts with organic bases.

6. Process for the preparation of salts of glycyrrhetinic acid according to any of Claims 1—4, substantially as hereinbefore described and with reference to any of the specific examples.

7. Salts of glycyrrhetinic acid according to any of Claims 1—4, whenever prepared by the process according to Claim 5 or 6.

8. Pharmaceutical and therapeutic compositions containing as active ingredient one or more glycyrrhetinic acid derivatives according to any of Claims 1—4 and 7, alone or in admixture with one or more antibiotics, keratoplastics, keratoplytics, analgesics, bactericides, chemotherapeutics, bacteriostatics, corticosteroids, xanthoglabrol, antihistaminics, sedatives, fungicides and/or insecticides, and an inert pharmaceutical carrier.

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We have now found that the salts formed from glycyrrhetinic acid and monoethanolamine, substituted monoethanolamines (such as choline) diethanolamine and isoniazide (i.e. isonicotinic acid hydrazide) are especially useful compounds. These new compounds may also be combined with other acids to give compounds such as isoniazide glycyrrhetinate monohydrochloride. Furthermore, in the case of the insoniazide derivatives, these may be further reacted in a known manner to give the corresponding hydrazones.

Medical, pharmacological, and veterinary tests and preliminary trials have been carried out with these new compounds on small and large animals, as well as pharmacological trials using mice, rats, guinea pigs and cats. These tests show that the new derivatives are active in suppressing inflammation, that they heal artificial lesions produced on the skin of animals and that they inhibit allergic reactions of injected allergens, such as aspergillus. When applied locally, these new compounds cause rapid subsidence of any inflammation produced by the introduction of irritant substances into the eye of the rabbit. When applied by systemic injection or by oral administration, these new compounds depress the formation of granuloma tissue induced by subcutaneously-implanted cotton wool pellets in rats in the tests described by Meier, R., Schuler W., and Desaulles, P., Experientia, 1950, 6, 469. These new derivatives depress the formation of inflammatory exudate and of the granulomatous membrane in the granuloma pouch test described by Selye, H., Brit. med. J., 1949, 2, 1129.

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treatment of ano-genital diseases, such as vulvitis, vaginitis, ulcerations of the vaginal basin and cervix of the uterus, either alone or in association with leucorrhoea, menstrual disfunctions, ano-genital pruritus, and in the treatment of diseases, such as carcinomas, in which the inhibition of steroids or the reduction of hormonal glandular secretion is of therapeutic value, as well as inflammatory and ulcerative conditions of the digestive system.

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